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(54) Method of treating shock using a potassium channel activator.

(57) A novel method for reducing or preventing impairment of cardiac and peripheral function resulting from shock is disclosed. The method comprises administering to a patient in need thereof a potassium channel activator.

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Shock is the term used generally to describe the various manifestations of an inadequate volume or a maldistribution of circulating blood accompanied by a series of progressively increasing physiologic adjustments, adverse to the cardiovascular system, which can lead to eventual refractoriness to treatment. Shock may be caused by blood loss, heart failure, burns, or other forms of trauma. A crucial element which 5 must be considered in the successful management of shock is that of cardiac impairment and subsequent peripheral ischemia.

In the shock syndrome a substantial decrease in blood volume causes decreased cardiac output and decreased blood pressure. Included in the various physiological responses triggered by the decreased cardiac output and decreased blood pressure are increased release of vasoconstrictors and catecholamines, 10 decrease in visceral and coronary blood flow and increased heart rate. The increased catecholamine and vasoconstrictor release and decreased coronary blood flow are believed to cause hypoxic conditions which can eventually result in necrotic subendocardial lesions. The increased heart rate along with the increased levels of catecholamines can also produce zonal lesions. The decreased visceral blood flow can result in release of a myocardial depressant factor. The necrotic and zonal lesions and release of myocardial 15 depressant factor, in turn, further compromise the heart, e.g., in the forms of arrhythmia, fibrillation, ischemia, etc., and this results in continuation of the aforementioned cycles which results in yet more pronounced lesions and depressant factor release, causing greater fibrillation, arrhythmia and ischemia, eventually resulting in cardiac failure and irreversible collapse of the cardiovascular system.

Some prevention of zonal lesions during shock can be provided by surgically-induced heart block, 20 administration of anti-beta-adrenergic agents, e.g., pronetholol, or cardiac denervation plus adrenalectomy. Necrotic lesions have been reportedly prevented by these same methods and also by hyperbaric oxygen treatment to avoid hypoxia.

Additional studies have shown the calcium channel blocker, verapamil, to provide improved cardiac function during shock. Verapamil is a vasodilator and lowers the heart rate. The vasodilatory effects are 25 believed to increase coronary blood flow resulting in enhanced supply of oxygen to the heart muscle. The decrease in heart rate is believed to lower oxygen demand. Therefore, prevention of necrotic myocardial lesions has been reported using verapamil during shock.

In addition to cardiac damage, peripheral damage occurs secondary to cardiac insufficiency due to maladistribution of blood. An ideal agent would protect both the heart and the periphery.

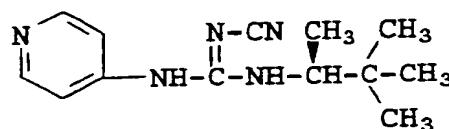
30 In accordance with the present invention a novel method for reducing or preventing the occurrence of cardiac and peripheral impairment during shock is disclosed. The method comprises the administration of an effective amount of a potassium channel activator to a mammalian specie in shock.

As is understood in the medical art and as described above, shock, as the term is used in describing the present invention, refers to the clinical manifestations of an inadequate volume of circulating blood 35 accompanied by the series of progressively increasing physiologic responses precipitated thereby, which responses are adverse to the cardiovascular system, including the heart. ATP-sensitive potassium channel openers have been shown to protect ischemic hearts and it has now been found that these agents also protect hearts during shock. Further, since ATP-sensitive potassium channels also exist in skeletal muscle and kidneys, which are often damaged during shock, these areas are protected as well. In practicing the 40 present method the potassium channel activator should be administered as soon as possible in the shock episode and continued throughout the period of shock and in the post-shock period for a time sufficient to ensure cardiac protection. Potassium channel activators have also been found to possess excellent antiischemic, antifibrillatory and antiarrhythmic activities which are believed to provide enhanced cardiac protection during and after the shock event.

45 In certain situations, such as in the treatment of patients in shock who are also affected with a previously-compromised heart/cardiovascular system, it may be desirable to provide protection to the heart against shock-induced myocardial lesions, fibrillation, arrhythmia and ischemia without lowering blood pressure and further compromising the heart/cardiovascular system. In a preferred embodiment of the present invention there is provided a method for treating shock providing the above-mentioned effects using 50 a selective potassium channel activator which has little or no vasodilatory activity and does not further reduce blood pressure.

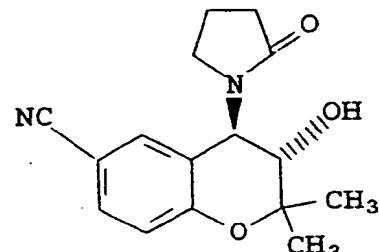
In addition to cardiac protection, potassium channel openers can protect skeletal muscle, brain and kidneys as these organs also possess potassium channels.

Any potassium channel activator may be used in accordance with the present invention. Suitable 55 potassium channel activators include those disclosed in U. S. Patent 4,057,636, especially the compound

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known as pinacidil; those disclosed in European Patent Application 0 274 821, especially the compound

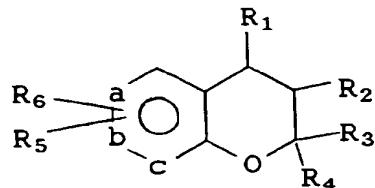
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B

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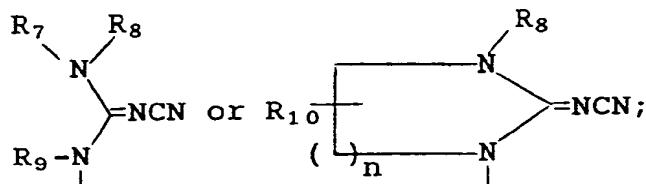
known as cromakalim; nicorandil; minoxidil; compounds in copending application U. S. Ser. No. 506,632 filed April 9, 1990 having the formula

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C

35 wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;
R₁ is

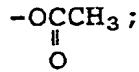
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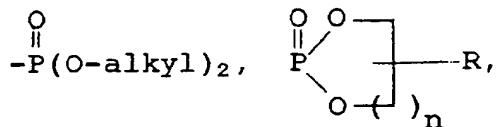
R₂ is hydrogen, hydroxy,

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R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or, R₃ and R₄ taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

55 R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl.



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halogen, amino, substituted amino, O-alkyl, OCF_3 , OCH_2CF_3 , -OCOalkyl, -OCNORalkyl, -NRCOOalkyl and NRCOOalkyl, NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

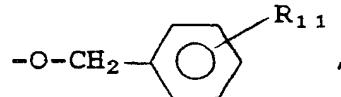
10 R₆ is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO₂;

R₇ and R₈ are each independently selected from hydrogen, alkyl, alkenyl, aryl, (heterocyclo)alkyl, heterocyclo, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R₇ and R₈ taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl;

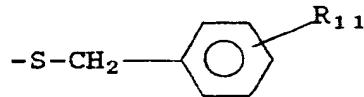
R₉ and R₁₀ are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; n is 1, 2 or 3; and,

wherein the term "aryl" refers to phenyl, 1-naphthyl, 2-naphthyl or monosubstituted phenyl, 1-naphthyl, 2-naphthyl wherein said substituent is alkyl of 1 to 4 carbons, alkylthio of 1 to 4 carbons, alkoxy of 1 to 4 carbons, halo, nitro, cyano, hydroxy, amino, -NH-alkyl wherein alkyl is of 1 to 4 carbons, -N(alkyl)₂ wherein alkyl is of 1 to 4 carbons, -CF₃, OCHF₂,

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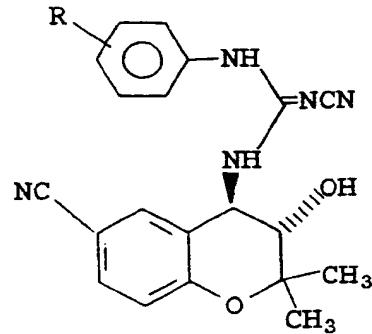
(wherein R₁₁ is hydrogen, alkyl of 1 to 4 carbons, alkoxy of 1 to 4 carbons, alkylthio of 1 to 4 carbons, halo, hydroxy or CF₃), -O-CH₂-cycloalkyl or -S-CH₂-cycloalkyl, and di-substituted phenyl, 1-naphthyl, 2-naphthyl wherein said substituents are selected from methyl, methoxy, methylthio, halo, CF₃, nitro, amino and OCHF₂;

40 with the compound

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C

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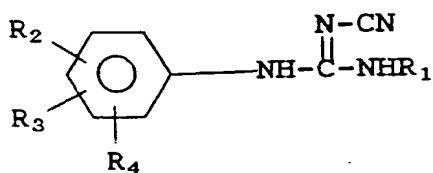
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(where R can be alkyl of 1 to 4 carbons, halo, nitro, cyano, hydroxy, amino, -NH-alkyl of 1 to 4 carbons or -N(alkyl)₂ where alkyl is of 1 to 4 carbons)

being preferred; compounds in copending application U. S. Ser. No. 349,021 filed May 8, 1989 having the

formula

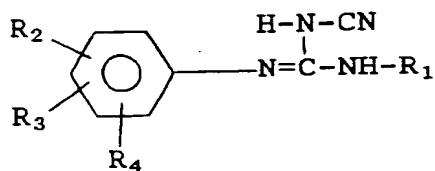
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D

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and its possible tautomers

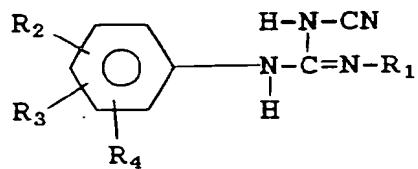
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D'

20

and

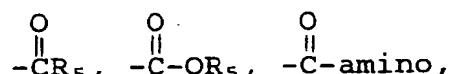
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D''

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wherein R₁ is alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, arylalkyl or cycloalkylalkyl;
R₂ is -C≡N, -NO₂,

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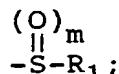
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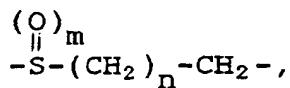
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-CF₃ or

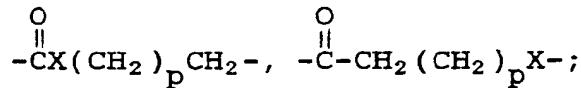
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R₃ and R₄ are each independently selected from -R₂, hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, halo, alkoxy, -NHalkyl, -N-(alkyl)₂, -S-alkyl, -O-arylalkyl, -S-arylalkyl or -S-aryl, -O-aryl, -NHarylalkyl, or R₂ and R₃ taken together are a group which forms a ring with the two carbon atoms to which they are attached, which group is selected from



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whcrcin

m = 1 or 2,

n = 1-3,

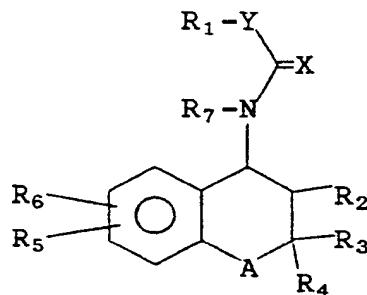
15 p = 0-2,

X is O, NR₅, CH₂; andR₅ is hydrogen or R₁;

compounds disclosed in copending patent application serial number 540,423 filed June 18, 1990 of the formula

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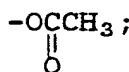
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wherein A can be -CH₂-, -O-, -NR₉, -S-, -SO- or -SO₂-, where R₉ is hydrogen or lower alkyl of 1 to 4 carbons;

35 wherein X is oxygen or sulfur;

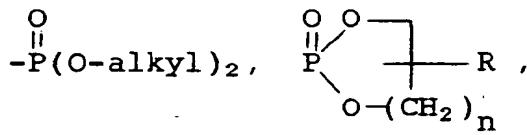
Y is -NR₈, -O-, -S- or

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R₁ is aryl, arylalkyl, heterocyclo or (heterocyclo)alkyl;45 R₂ is hydrogen, hydroxy,

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R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or, R₃ and R₄ taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;55 R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl,



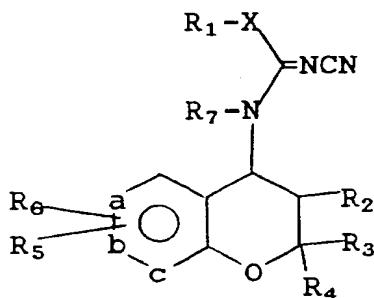
halogen, amino, substituted amino, O-alkyl, OCF_3 , OCH_2CF_3 , -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

10 R₆ is selected from H, alkyl, halo, OH, O-alkyl, amino and substituted amino;
 R₇ and R₈ are each independently selected from hydrogen, alkyl, arylalkyl;
 n is 1, 2 or 3; and,
 R₁₀ is hydrogen, hydroxy, alkyl or O-alkyl; and compounds in copending application Serial No. 502,967 filed April 2, 1990 having the general formula

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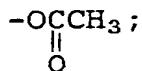
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F

wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons; where X is oxygen or sulfur;

30 R₁ is selected from aryl, arylalkyl, (heterocyclo)alkyl, heterocyclo, cycloalkyl and (cycloalkyl)alkyl.
 R₂ is hydrogen, hydroxy,

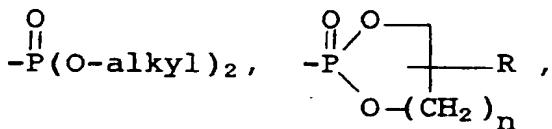
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40 R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or, R₃ and R₄ taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl,

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halogen, amino, substituted amino, O-alkyl, OCF_3 , OCH_2CF_3 , -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R₆ is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO₂;
 R₇ is selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and,
 n is 1, 2 or 3.

In carrying out the method of the present invention, the potassium channel activator may be administered to mammalian species, such as monkeys, dogs, cats, rats, humans, etc., during the period of shock.

The potassium channel activator may be administered systemically, such as orally or parenterally, or the potassium channel activator be administered locally to the coronary arteries by catheter such as by arterial angiography or intracoronary injection.

The potassium channel activator may be incorporated in a conventional dosage form, such as a tablet, 5 capsule, elixir or injectable. The above dosage forms will also include the necessary carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

With regard to such systemic formulations, single or divided doses of from about 5 to about 2500 mg, 10 preferably from about 10 to 2000 mg/one to four times daily, may be administered in systemic dosage forms as described above for a period sufficient to reduce and avoid impairment of cardiac function resulting from the shock event.

With regard to dosage of potassium channel activator, where the drug is administered by arterial angiography or intracoronary injection, from about 0.001 to about 30 mg/kg/treatment and preferably from 15 about 0.5 to about 25 mg/kg/treatment will be employed. The number of treatments will depend upon the severity of the fibrillation and the progress of reperfusion to achieve normal heart rhythm. Usually, from 1 to 5 treatments per day will be required for as long as fibrillation continues.

Where the potassium channel activator is to be administered by angiography or intracoronary injection, it will be formulated in a conventional vehicle, such as distilled water, saline, Ringer's solution, or other 20 conventional carriers.

The preferred method of the present invention involves using compounds of the general formulae C, E or F to maintain cardiac function during and after shock without lowering blood pressure. Compounds of formula C, E or F are useful in the parent method where no antihypertensive action is desired. Such "selective" compounds are those potassium channel activators which have IC₅₀ (rat aorta) values greater 25 than that of cromakalim. These include compounds of formula C where R₇ is (or compounds of formula E or F where R₁ is) aryl, arylalkyl, heteroaryl or heteroarylalkyl.

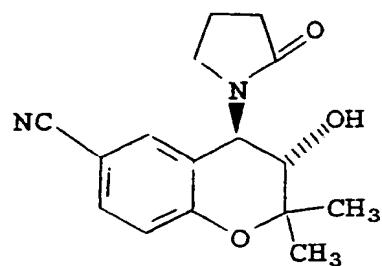
Grover et al., "Dissociation of Cardiodepression from Cardioprotection with Calcium Antagonists: Diltiazem Protects Ischemic Rat Myocardium with a Lower Functional Cost as Compared with Verapamil and Nifedipine", *Journal of Cardiovascular Pharmacology*; pages 331-340, Vol. 14, No. 2 (1989), describe a 30 model for testing globally ischemic, isolated rat hearts. This model is expected to be a reliable indicator of protection since the laboratory-induced isolation and ischemic event including perfusion with a cardioplegic solution, reasonably duplicates the environment and conditions for the heart during and after a shock or trauma episode. Grover et al. express the efficacy of protective agents as the amount of lactate dehydrogenase (LDH) release and post-ischemic cardiac function.

Lactate dehydrogenase is an enzyme released in the heart during an ischemic event and is an index of 35 cardiac cell necrosis. In the Grover et al. model, this is measured during reperfusion and an agent which provides for lower release levels of LDH is considered to offer greater cardioprotection since lower LDH indicates a smaller infarct size. Cardiac function is determined using the double product (DP) of heart rate times the left ventricular developed pressure (LVDP) divided by 1,000.

The lower the value for DP before the ischemic isolation of the heart for a given agent, the more 40 cardiodepressant it is considered to be and the higher the value of DP is during reperfusion, the more cardioprotective the agent is.

The following Example examines cromakalim, a potassium channel activator having vasodilator/blood pressure lowering activity, and compounds from formula C, E and F, which have little or no vasodilating 45 activity in normal tissue.

Compounds Tested in Example



Cromakalim

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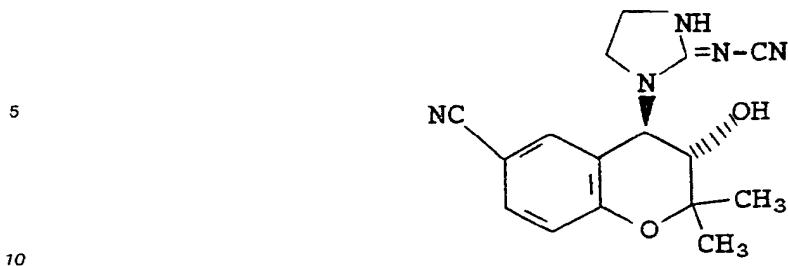
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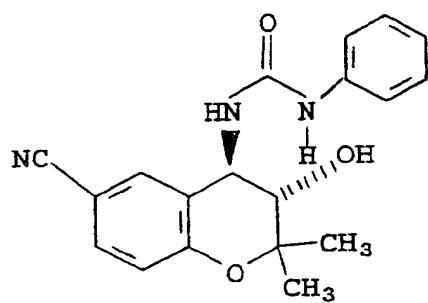
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C''

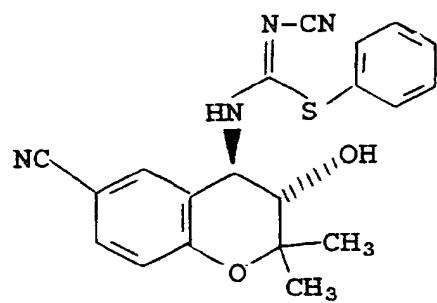
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E''

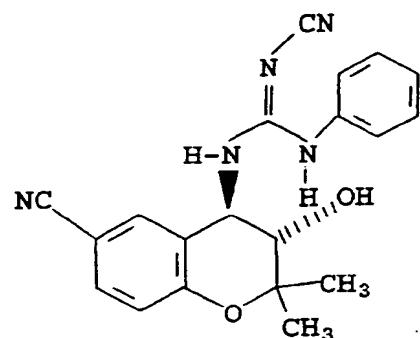
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F''

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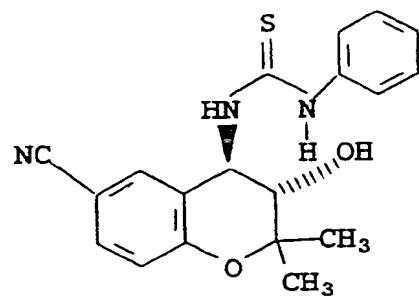
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C'

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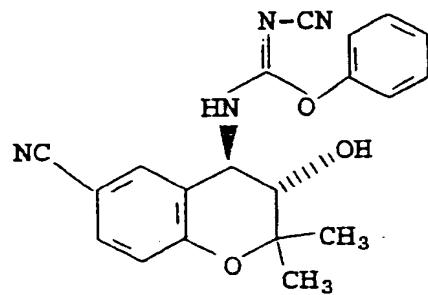
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E'

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F'55 EXAMPLEPreparation of the Isolated Perfused Hearts

Male Sprague-Dawley rats (450-550 g) were used in all experiments. The rats were anesthetized using 30 mg/kg sodium pentobarbital (i.p.). They were intubated and then treated with i.v. heparin (1000 U/kg). While being mechanically ventilated, their hearts were perfused *in situ* via retrograde cannulation of the aorta. The hearts were then excised and quickly moved to a Langendorff apparatus where they were 5 perfused with Krebs-Henseleit bicarbonate buffer (112 mM NaCl₂, 25 mM NaHCO₃, 5 mM KCl, 1.2 mM MgSO₄, 1 mM KH₂PO₄, 1.25 mM CaCl₂, 11.5 mM dextrose, and 2 mM pyruvate bubbled with 95% O₂ - 10 5% CO₂) at a constant pressure (75 mm Hg). A water filled latex balloon attached to a metal cannula was then inserted into the left ventricle and connected to a Statham pressure transducer for measurement of left ventricular pressure. The hearts were allowed to equilibrate for 15 minutes at which time end diastolic 15 pressure (EDP) was adjusted to 5 mm Hg and this was maintained for 5 minutes. Pre-ischemia or pre-drug function, heart rate and coronary flow (extracorporeal electromagnetic flow probe, Carolina Medical Electronics, King, N.C.) were then measured. Cardiac function was determined using the double product of heart rate (HR) X left ventricular developed pressure (LVDP) divided by 1000. Cardiac temperature was maintained throughout the experiment by submerging the hearts in 37°C buffer which was allowed to accumulate in a stoppered, heated chamber.

Experimental Protocol

Once the baseline measurements were taken, the hearts were treated with 10 μM cromakalim, 20 compounds C', C'', E', E'', F', F'' (n = 4 each) or with vehicle buffer (0.01% DMSO, n = 7). All of these hearts were treated with their respective drugs or vehicle for ten minutes. At this time, post-drug cardiac function and flow were measured and then the hearts were made globally ischemic by shutting off the buffer perfusion. The ischemia was maintained for 25 minutes, the hearts were then reperfused with nondrug treated buffer. Reperfusion was maintained for a total of 30 minutes and at this time reperfusion 25 function and flow were again determined. The results are summarized in the TABLE below.

Also included in the TABLE are the IC₅₀(m) values for rat aorta. The IC₅₀ (rat aorta) value is the concentration of the particular compound which inhibits agonist-induced constriction in rat aorta by 50 percent. Thus, the lower values indicate greater vasodilation and it should be noted that these values are for normal, i.e., non-ischemic, tissue. It can be seen that cromakalim with an IC₅₀ of 5.7 × 10⁻⁸ m is a relatively 30 potent vasodilator in non-ischemic tissue. The ischemia selective compounds, however, are comparable in the anti-ischemic effects (LDH) but have only a fraction of the vasodilator action in non-ischemic tissue.

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TABLE
Protective Effect of Potassium Channel Activators

Event (Post Drug)	Ischemic Isolated Rat Heart						IC_{50} (m) Rat Aorta			
	Pre-ischemic			Reperfusion						
(Post-Ischemic Event)	HR	LVDP	DP	FLOW	HR	LVDP	DP	FLOW	LDH	
Vehicle	245	144	35.5	15.5	186	28	5.6	14.7	21.94	---
Cromakalim	250	131	33.0	23.9	234	87	20.5	13.9	8.89	5.7×10^{-8}
C ^I "	244	134	32.7	15.2	244	74	18.2	13.2	10.41	1.37×10^{-6}
C ^{II} "	250	121	29.8	20.4	240	62	14.8	10.1	9.88	4.47×10^{-7}
E'	236	141	32.75	15.3	229	55	14.83	13.4	13.46	1.71×10^{-6}
E ^{II} "	234	128	30.06	24.8	230	81	18.52	17.56	8.77	8.05×10^{-7}
F'	238	128	30.5	16.0	212	28	6.2	10.4	21.7	$>1 \times 10^{-4}$
F ^{II} "	239	159	38.02	28.3	247	59	14.72	13.92	10.65	4.9×10^{-6}

Concentration: 10 μ M
Occlusion: 25 minutes
Reperfusion: 30 minutes

HR = Heart Rate

LVDP = Left Ventricular Developed Pressure (mmHg)

DP = Double Product

LDH = Lactate Dehydrogenase Release

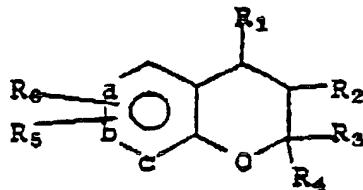
Claims

55 1. Use of a potassium channel activator for preparing a medicament for reducing or preventing the impairment of cardiac function caused by shock in a mammalian specie in need thereof.

2. The use of claim 1 wherein said potassium channel activator is for administration as soon as possible after initiation of the shock occurrence with said administration to be continued for a time sufficient to ensure cardiac and peripheral protection.

5 3. The use of claim 1 wherein said potassium channel activator is selected from nicorandil, minoxidil, pinacidil, cromakalim and compounds of the formula

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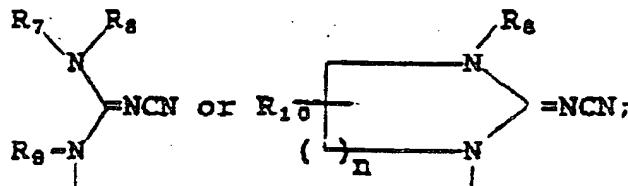
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wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

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R₁ is

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R₂ is hydrogen, hydroxy,

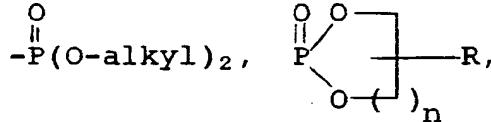
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R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or, R₃ and R₄ taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

40 R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SO₂alkyl,

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halogen, amino, substituted amino, O-alkyl, OCF₃, OCH₂CF₃, -OCOOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

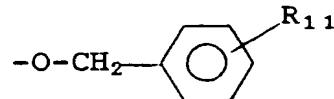
45 R₆ is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO₂;

R₇ and R₈ are each independently selected from hydrogen, alkyl, alkenyl, aryl, (heterocyclo)alkyl, heterocyclo, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R₇ and R₈ taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiomorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl;

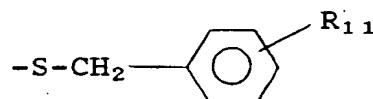
R₉ and R₁₀ are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; n is 1, 2 or 3; and,

wherein the term "aryl" refers to phenyl, 1-naphthyl, 2-naphthyl or monosubstituted phenyl, 1-naphthyl, 2-naphthyl wherein said substituent is alkyl of 1 to 4 carbons, alkylthio of 1 to 4 carbons, alkoxy of 1 to 4 carbons, halo, nitro, cyano, hydroxy, amino, -NH-alkyl wherein alkyl is of 1 to 4 carbons, -N(alkyl)₂ wherein alkyl is of 1 to 4 carbons, -CF₃, OCHF₂,

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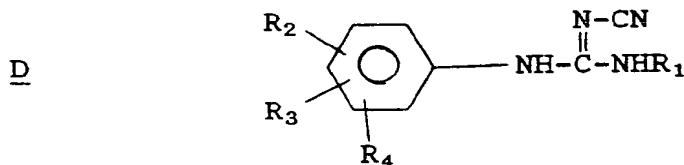


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(wherein R₁₁ is hydrogen, alkyl of 1 to 4 carbons, alkoxy of 1 to 4 carbons, alkylthio of 1 to 4 carbons, halo, hydroxy or CF₃), -O-CH₂-cycloalkyl or -S-CH₂-cycloalkyl, and di-substituted phenyl, 1-naphthyl, 2-naphthyl wherein said substituents are selected from methyl, methoxy, methylthio, halo, CF₃, nitro, amino and OCHF₂;

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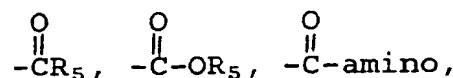
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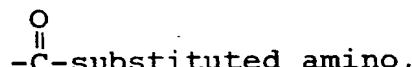
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wherein R₁ is alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, arylalkyl or cycloalkylalkyl; R₂ is -C≡N, -NO₂,

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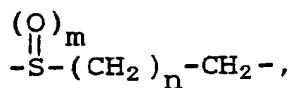


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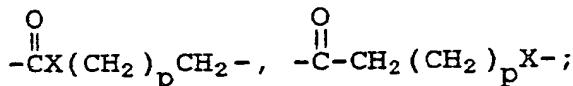


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R₃ and R₄ are each independently selected from -R₂, hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, halo, alkoxy, -NHalkyl, -N-(alkyl)₂, -S-alkyl, -O-arylalkyl, -S-arylalkyl or -S-aryl, -O-aryl, -NHarylalkyl, or R₂ and R₃ taken together are a group which forms a ring with the two carbon atoms to which they are attached, which group is selected from



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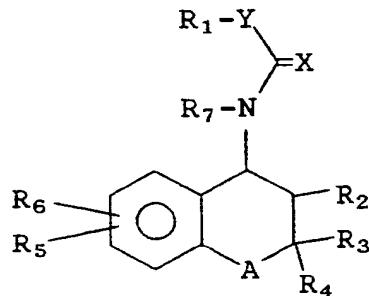


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wherein

 $m = 1$ or 2 , $n = 1$ - 3 , $p = 0$ - 2 , X is O , NR_5 , CH_2 ; and R_5 is hydrogen or R_1 ;

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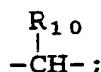
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wherein A can be $-\text{CH}_2-$, $-\text{O}-$, $-\text{NR}_9-$, $-\text{S}-$, $-\text{SO}-$ or $-\text{SO}_2-$, where R_9 is hydrogen or lower alkyl of 1 to 4 carbons;wherein X is oxygen or sulfur;

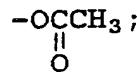
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 Y is $-\text{NR}_8$, $-\text{O}-$, $-\text{S}-$ or

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 R_1 is aryl, arylalkyl, heterocyclo or (heterocyclo)alkyl; R_2 is hydrogen, hydroxy,

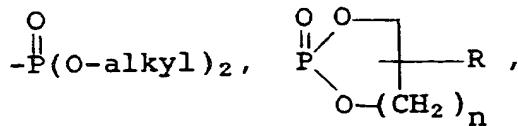
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 R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring; R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{COR}$, $-\text{COOR}$, $-\text{CONHR}$, $-\text{CONR}_2$, $-\text{CF}_3$, S-alkyl, $-\text{SOalkyl}$, $-\text{SO}_2\text{alkyl}$,

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halogen, amino, substituted amino, O-alkyl, OCF_3 , OCH_2CF_3 , -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R₆ is selected from H, alkyl, halo, OH, O-alkyl, amino and substituted amino;

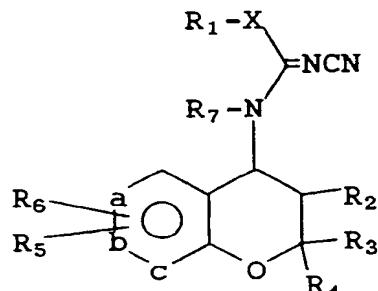
5 R₇ and R₈ are each independently selected from hydrogen, alkyl, arylalkyl;

n is 1, 2 or 3; and,

R₁₀ is hydrogen, hydroxy, alkyl or O-alkyl; and

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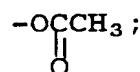
wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

where X is oxygen or sulfur;

20 R₁ is selected from aryl, arylalkyl, (heterocyclo)alkyl, heterocyclo, cycloalkyl and (cycloalkyl)alkyl.

R₂ is hydrogen, hydroxy,

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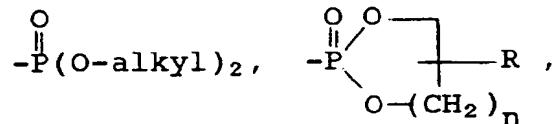
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R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or, R₃ and R₄ taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

35

R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl,

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halogen, amino, substituted amino, O-alkyl, OCF_3 , OCH_2CF_3 , -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R₆ is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO₂;

R₇ is selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and,

n is 1, 2 or 3.

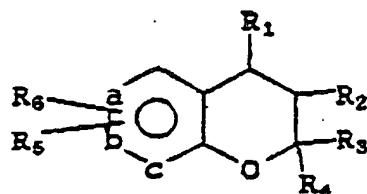
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4. The use of claim 1 wherein said potassium channel activator has an IC₅₀ (rat aorta) value greater than said value for the potassium channel activator, cromakalim.

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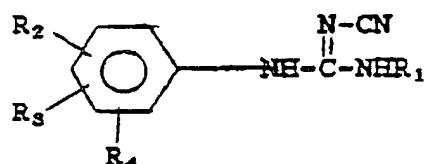
5. The use of claim 4 wherein said potassium channel activator is selected from

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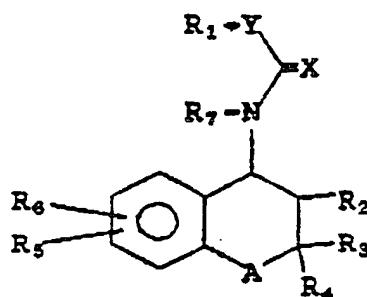
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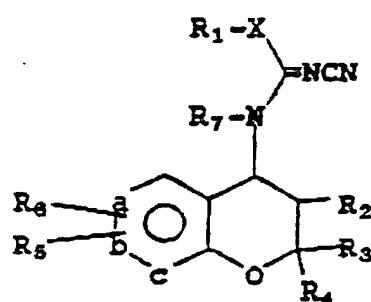
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or

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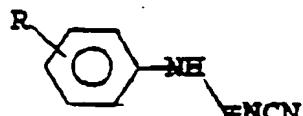


50 6. The use of claim 5 wherein said potassium channel activator is

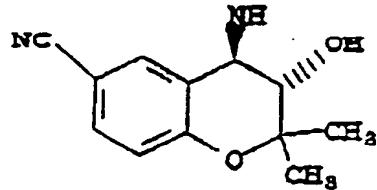
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C' "

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where R can be alkyl of 1 to 4 carbons, halo, nitro, cyano, hydroxy, amino, -NH-alkyl of 1 to 4 carbons or -N(alkyl)₂ where alkyl is of 1 to 4 carbons.

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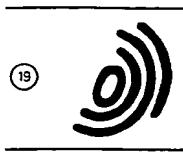
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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) Publication number:

0 489 404 A3

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 91120768.6

(51) Int. Cl.5: **A61K 31/00, A61K 31/35,**
A61K 31/40, A61K 31/415

(22) Date of filing: 03.12.91

(30) Priority: 05.12.90 US 622679

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(43) Date of publication of application:
10.06.92 Bulletin 92/24

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(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

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(54) Method of treating shock using a potassium channel activator.

(57) A novel method for reducing or preventing impairment of cardiac and peripheral function resulting from shock is disclosed. The method comprises administering to a patient in need thereof a potassium channel activator.

EP 0 489 404 A3



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

Application Number

EP 91 12 0768

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
X	DRUG DEVELOPMENT RESEARCH, vol. 19, no. 1, 1990, pages 91-97, Wiley-Liss, Inc.; T. HAMAGUCHI et al.: "Cardioprotective effects of nicorandil on calcium paradox-induced injury" * Paragraph: "Discussion" *	1,2,3	A 61 K 31/00 A 61 K 31/35 A 61 K 31/40 A 61 K 31/415
X	EP-A-0 351 767 (SQUIBB) * Entire document *	1,2,3,4	
X	RESPIRATION AND CIRCULATION, vol. 37, no. 11, November 1989, pages 1231-1235; J. HAYASHI et al.: "Protective effects of nicorandil against catecholamine induced myocardial damage under hypoxia" * Page 1235, abstract *	1,2,3,4	
P,X	EP-A-0 401 010 (SQUIBB) * Claims; page 11 *	1-6 -/-	TECHNICAL FIELDS SEARCHED (Int. Cl. 5) A 61 K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

Claims searched completely:

Claims searched incompletely: 2, 4

Claims not searched:

Reason for the limitation of the search:

1. It is not clear which mode of administration is meant (claim 2)
2. A compound cannot be sufficiently described by its pharmacological effect (claim 4)

Place of search	Date of completion of the search	Examiner
THE HAGUE	15-07-1992	KLAVER T.
CATEGORY OF CITED DOCUMENTS		
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		

T : theory or principle underlying the invention
 E : earlier patent document, but published on, or after the filing date
 D : document cited in the application
 L : document cited for other reasons
 & : member of the same patent family, corresponding document



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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid.
namely claims:
- No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,
namely:

see sheet -B-

- All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid.
namely claims:
- None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.
namely claims:



PARTIAL EUROPEAN SEARCH REPORT

Application Number

EP 91 12 0768

DOCUMENTS CONSIDERED TO BE RELEVANT		CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
A	TRENDS IN PHARMACOLOGICAL SCIENCE, vol. 9, January 1988, pages 21-28, Elsevier Publications, Cambridge, GB; N.S. COOK: "The pharmacology of potassium channels and their therapeutic potential" ---	
A	CIRCULATIONS RESEARCH, vol. 62, no. 4, April 1988, pages 679-686; R.P. HOF et al.: "Mechanism of action and systemic and regional hemodynamics of the potassium channel activator BRL34915 and its enantiomers" ---	
A	AMERICAN JOURNAL OF PHYSIOLOGY, vol. 259, no. 2, part 2, August 1990, pages F348-F356, The American Physiological Society; L. DUBE et al.: "Hypotonic shock activated a maxi K ⁺ channel in primary cultured proximal tubule cells" ---	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A	EP-A-0 389 861 (FUJISAWA) ---	
A	EP-A-0 359 537 (BEECHAM) ---	
A	EP-A-0 344 747 (FUJISAWA) -----	



European Patent
Office

EP 91 12 0768 -B-

LACK OF UNITY OF INVENTION a posteriori

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims 1,2,3 in part,4: Use of nicorandil against the impairment of cardiac function due to shock.
2. claim 3 in part: Use of minoxidil against the impairment of cardiac function due to shock.
3. claim 3 in part. Use of pinacidil against the impairment of cardiac function due to shock.
4. claim 3 in part: Use of cromakalim against the impairment of cardiac function due to shock.
5. claims 3,5,in part,6: Use of a compound of formula C,E or F against the impairment of cardiac function due to shock.
6. claims 3,5 in part: Use of a compound of formula D, against the impairment of cardiac function due to shock.

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